UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,078	12/31/2001	Mark H. Tuszynski	041673-2053	9151

30542 7590 08/01/2005

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,078	TUSZYNSKI, MARK H.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The responses filed January 31, 2005 and April 26, 2005 have been entered. Claims 17 and 18 have been newly added.

Applicant's election without traverse of Group I, Claims 6-8, in the reply filed on January 31, 2005 is acknowledged. The elected invention is drawn to a method for delivery of a therapeutic nervous system growth factor to cortical tissue, wherein a recombinant expression vector encoding a nervous system growth factor is administered to the subject (gene therapy). Claims 1-5 and 9-16 link the inventions of Groups I and II.

Applicant further elected, with traverse, the species of nerve growth factor (NGF) for examination.

The traversal is on the grounds that no undue burden would be imposed on the Examiner in examining all species together, because the subject matter is inter-related. This is not found persuasive because, the presence of inter-related subject matter is not sufficient to preclude "undue burden." The species are distinct both structurally and functionally. These factors clearly indicate a serious burden. Thus, search and examination of all species in a single patent application constitutes a serious burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the election of species requirement in the reply filed on January 31, 2005.

Accordingly, Claims 1, 2, and 6-18 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1, 2, and 6-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendments to the claims include new matter.

Newly added Claim 17 is directed to a method of using NGF, wherein the NGF is delivered to neurons in cortical tissues containing trkB receptors. However, the as-filed specification does not contemplate delivering NGF to "cortical tissues containing trkB receptors." As support for newly added Claim 17, Applicant points to the specification at page 5, lines 11-21 (see the remarks at page 5 of the response filed January 31, 2005). Contrary to Applicant's assertion, however, the cited section only refers to NGF as being a nervous system growth factor known in the prior art. Neither the cited section nor the remainder of the specification contemplate delivering NGF to "cortical tissues containing trkB receptors." Quite contrary to the instantly claimed invention, the specification explicitly states that "the invention pertains to the use of growth factors that activate the trkB nervous system growth factor receptor (including brain-derived neurotrophic factor (BDNF) and nervous system growth factor-4/5 (NT-4/5)) to stimulate neuronal activity in the entorhinal cortex (EC)" (emphasis added, page 1, lines 8-11). It is well-known in the prior art that NGF binds to and activates the trkA receptor, not the trkB receptor.

See, for example, Levi-Montalcini et al. (1996) which discloses that NGF binds to the trkA receptor (page 514, column 1, paragraph 2).

The instantly claimed invention is far-removed from the invention described in the as-filed specification because the specification does not contemplate using growth factors that do not activate the trkB receptor. Further, the specification does not contemplate delivering NGF to the entorhinal cortex, as required in Claim 9. Likewise, the specification does not contemplate a lentiviral vector encoding NGF, as required by Claims 7 and 8. The examples of the specification are exclusively directed to investigating the effects of BDNF.

In view of the election of species directed to NGF and newly added Claim 17 which depends from Claim 1, Claims 1, 2, 6-16, and 18, encompass delivering NGF to cortical tissues containing trkB receptors. Absent specific support in the as-filed specification, the newly claimed subject matter constitutes new matter.

Thus, the amended claims include new matter.

Enablement

Claims 1, 2, and 6-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the

claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the Invention and Scope of the Claims. The claims are directed to a method for delivery of a therapeutic nervous system growth factor to targeted defective, diseased or damaged neurons in cortical tissues containing trkB receptors, the method comprising delivering a nervous system growth factor composition into one or more delivery sites within the targeted cortical tissues of a subject; wherein contact with the nervous system growth factor ameliorates the defect, disease or damage in the subject's cortical cells, including those in the entorhinal cortex (EC).

The claims encompass treatment of a huge variety of diseases of the central nervous systems (CNS). The claims cover the treatment of disorders in which any type of cell of the nervous system has been injured or has degenerated. In the central nervous system alone, a great variety of different cell types are present, including hundreds of different types of neurons, astrocytes, oligodendrocytes, microglia, epithelial cells, endothelial cells, immune system cells that have entered the brain and spinal cord tissue, blood vessels and blood cells that feed the tissues, stem cells, etc. Thus, the claims cover the treatment of a wide variety of different types of disorders, including psychiatric disorders, motor disorders, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Kallmann syndrome, the spinocerebellar ataxias, spinal cord injury, head trauma, stroke, developmental disorders, etc., to name just a few. Thus, the claims are very broad in scope with regard to the type of disease to be treated. However, the specification itself only contemplates using the claimed invention to treat Alzheimer's disease or broadly to treat "neurodegenerative disease and aging" (page 1, lines 6-7). The claims cover delivering any type of polynucleotide (naked DNA, plasmid vector, viral vector, etc.) encoding a wide variety of protein products, including NGF, to any region of the brain, via any route of delivery. Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be

achieved by the method. Claim 1 requires no clinical amelioration, only that contact with the nervous system growth factor "ameliorates the defect, disease or damage in the subject's cortical cells, including those in the entorhinal cortex (EC)."

Amount of direction or guidance presented and the presence or absence of working examples. Although the specification provides several examples relating to BDNF, the specification does not provide any examples relating to the *in vivo* administration of a vector encoding NGF to a diseased animal, and moreover does not provide any examples relating to the use of NGF polynucleotides in gene therapy applications. Neither the specification nor the prior art provides any teaching with regard to the *in vivo* activity of a NGF-encoding vector in "cortical tissues containing trkB receptors," particularly in a disease context. The specification does not provide any guidance for delivering an NGF-encoding vector to a cell containing trkB receptors. NGF binds to the trkA receptor and neither the prior art nor the instant specification teach that NGF should be delivered to cells that do not express the trkA receptor. The claims, however, clearly encompass delivering NGF to cells that do not express the trkA receptor.

With regard to gene therapy the specification provides only limited and general guidance (page 4, paragraph 1; page 6, paragraph 3; pages 7-9; Example VIII). The specification fails to provide any **specific guidance** on the generation of the nucleic acid construct to be used in the gene therapy method or on the targeting of neurological tissue for the treatment of any specific neurological or neurodegenerative disorder.

State of the prior art and predictability of the art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely achievable by those skilled in the art. This is reflected in numerous references. Verma et al. (1997) disclose that "there is still no single outcome that we can point to as a success story" (page 239, column 1). The authors go on to state "[t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, column 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-

therapy protocol has been successful in the treatment of a human disease" (page 25, column 1) and concludes that "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (page 30). The instant specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for the breadth of the claimed invention. Numerous factors complicate the gene delivery art which cannot be overcome by routine experimentation. These include the fate of the DNA vector itself (volume of distribution, rate of clearance in the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. Hodgson (1995) discusses the drawbacks of viral transduction and chemical transfection methods and states that "[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pages 459-460). Miller et al. (1995) also review the types of vectors available for *in vivo* gene delivery and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). In the instant application, the specification provides no teachings on the generation of the nucleic acid construct to be used in a gene therapy method nor on the targeting of the appropriate neurological tissue for the various diseases to be treated. In the absence of specific guidance, the skilled artisan would have been required to develop successful protocols for practicing the claimed methods over a very large and improbable scope, without guidance on a starting point or the direction in which experimentation should proceed. However, given that the gene therapy art was considered highly unpredictable and undeveloped, the skilled artisan

would have been required to engage in undue experimentation to come up with successful gene therapy protocols.

The claims encompass a wide variety of neurodegenerative diseases. Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract).). Kumar et al. (1992) discloses that "[u]nlike other categories of disease such as infections or trauma that may share etiological origins, the degenerative diseases are unified only by some general clinicopathologic features. Currently, almost all are of obscure origin, and there is no compelling reason to suppose that they have the same, or even a similar type of cause" (pages 725-726). A wide variety of therapeutic strategies for the treatment of neurodegenerative diseases are being pursued. However, despite intensive effort on the research front, the existence of successful treatment protocols was extremely limited in 2001.

The claims encompass a wide variety of polynucleotides encoding a wide variety of protein molecules for the treatment of any CNS disorder. However, given that the gene therapy art is highly unpredictable and further given that the specification fails to provide specific guidance on which nucleic acids encoding which protein can be used to treat a specific neurodegenerative disease of interest, across the very broad scope, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any particular neurodegenerative disease.

In an article published around the filing date of the instant application and well after the effective filing date, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems

with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pages 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of vector types to treat a wide variety of neurodegenerative diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation.

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166

USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the limited examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon *in vivo* administration of a polynucleotide agent as recited in the claims, the very broad scope of the claims, and the unpredictability for producing a therapeutic effect upon administration of a polynucleotide agent as recited in the claims, undue experimentation would have been required for one skilled in the art to develop a protocol within the scope of the claims for treating a wide variety of neurodegenerative diseases, and moreover to develop protocols across the full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 6, and 11-17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,451,306 (Tuszynski et al., filed April 15, 1998).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Tuszynski et al. (1998) discloses grafting cells that express nerve growth factor into the brain of a primate for treatment of Alzheimer's disease. The donor cells are genetically modified by insertion of a transgene encoding a nerve growth factor, particularly nerve growth factor (NGF) itself. See especially Claims 1 and 3. The specification contemplates using a recombinant expression vector to deliver the gene to the donor cells (Columns 5-6).

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER